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(71) Applicant *(for all designated States except US)*: MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: MITCHEL, Yale, B. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). TOBERT, Jonathan, A. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

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(54) Title: METHOD FOR TREATING HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

(57) Abstract

Homozygous familial hypercholesterolemia can be treated in patients suffering with this condition by administering a therapeutically effective amount of simvastatin. Dosages above 40 mg/day, and more particularly at or above 80 mg/day, were found to effectively reduce the LDL cholesterol levels in these patients.

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Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
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EE	Estonia	LR	Liberia	SG	Singapore		

TITLE OF THE INVENTION

METHOD FOR TREATING HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

RELATED APPLICATIONS

This application is a continuing application and claims priority to U.S. provisional application number 60/021,420, filed July 9, 1996, and to U.S. provisional application number 60/029,351, filed October 31,1996.

BACKGROUND OF THE INVENTION

Homozygous familial hypercholesterolemia (HFH) is a rare disorder characterized by the presence of two abnormal low density lipoprotein (LDL) receptor genes which results in the patient having dysfunctional LDL receptors. This results in severe hypercholesterolemia, particularly extreme elevations in LDL levels, and rapid development of coronary atherosclerosis and coronary heart disease in those who suffer with HFH. Most patients develop coronary disease in adolescence and usually do not survive beyond their teen-age years.

HMG-CoA reductase inhibitors such as compactin, lovastatin, simvastatin, pravastatin, etc., are believed to work by upregulating LDL receptor activity and increasing LDL removal from the blood. Since FH homozygotes do not have functional LDL receptors, this class of drugs was generally believed to be ineffective in these patients. Previous experience with HMG-CoA reductase inhibitors in FH homozygote children bore this out. For example, in J. Thiery, et al., *European Journal of Pediatrics*, (1990) *149*: 716-721, it is noted that compactin, at dosages as high as 200 mg per day, and lovastatin caused only marginal lowering of LDL cholesterol levels in HFH patients and therefore were not considered to be useful therapies for this condition.

The treatment options available to those suffering with HFH have been limited to liver transplantation or LDL aphaeresis therapy. LDL aphaeresis is a technique where plasma is removed from patients

and run over columns either with an antibody to apo B or reagents to precipitate LDL. It is usually performed once every two weeks in this population with about a 70% reduction in LDL cholesterol immediately after the procedure, with levels returning to baseline at one week post-treatment. Both treatment options are associated with considerable morbidity and are in limited supply.

More recently, a second-generation HMG-CoA reductase inhibitor, atorvastatin, has been shown to be useful for treating HFH.

Contrary to what was previously believed due to the nature of HFH and the mechanism of action understood to be associated with HMG-CoA reductase inhibitors as well as the available published studies in this field, it has been discovered that simvastatin (marketed in the U.S. under the trademark ZOCOR®) in doses above 40 mg per day can be used to treat patients suffering with HFH.

SUMMARY OF THE INVENTION

The main object of the instant invention is to provide a method for treating homozygous familial hypercholesterolemia comprising administering a therapeutically effective amount of simvastatin to a person in need of such treatment. A person in need of such treatment is one who has homozygous familial hypercholesterolemia. Additional objects will be evident from the following detailed description.

DETAILED DESCRIPTION OF THE INVENTION

It has been found that simvastatin in daily dosages above 40 mg are useful for the treatment of HFH. Preferably, the daily dosage is at least 80 mg, and more preferably, at least 160 mg. The compound may be administered in a single daily dose, or divided doses, for example two, three or four times daily. Simvastatin may also be administered in a sustained release formulation, for example employing the formulation described in U.S.Patent No. 5,366,738. Sustained release and daily divided dose administration is preferred.

The following study results demonstrate the usefulness of simvastatin in the treatment of HFH.

I. Study Design

Design: double blinded, randomized, parallel, dose-escalation, controlled, 18 week study

Patients: 12 patients with well-characterized HFH

Treatment: After a 4 week placebo diet run in period, the 12 patients were randomized to simvastatin (S) 80 mg/day (group 1, n=8) or 40 mg/day (group 2, n=4). After 9 weeks, the dose in group 1 was increased to 160 mg/day while the dose in group 2 was kept at 40 mg/day and treatment continued for an additional 9 weeks. Simvastatin was administered orally. The simvastatin treatment information is summarized in the table, below.

	Period 1 (9 weeks)	Period 2 (9 weeks)
Group 1 (n=8):	80 mg/day in 3 divided doses	160 mg/day in 3 divided doses
Group 2 (n=4):	40 mg/day once a day	40 mg/day in 3 divided doses

Endpoint: Change in low density lipoprotein cholesterol

II. Study Results

The results of the study are as follows. For T-C, LDL-C and HDL-C, mean baseline and mean % change from baseline are shown; for TRIG, median baseline and median % change from baseline are shown:

	GROUP 1 (n=8)			GROUP 2 (n=4)		
	BL (mg/dl)	80 mg/day tid dosing % change	160 mg/day tid dosing % change	BL (mg/dl)	40 mg/day hs % change	40 mg/day tid dosing % change
T-C	627	-23	-29	562	-12	-13
LDL-C	570	-25	-31	519	-14	-15
TRIG	136	-9	-15	72	7	-11
HDL-C	32	12	6	28	11	17

BL = baseline
T-C = total cholesterol
LDL-C = low density lipoprotein cholesterol
TRIG = triglyceride level
HDL-C = high density lipoprotein cholesterol

All 12 patients completed the trial and there were no serious or unexpected adverse events. No patients sustained significant hepatic transaminase or creatine kinase elevations.

As can be seen from the above study results, simvastatin at therapeutically effective doses of 80 mg/day and higher is effective in lowering LDL-C in patients suffering with homozygous familial hypercholesterolemia.

As such, simvastatin may be administered as monotherapy to a patient suffering with HFH, or it may be administered in combination with other therapies which are suitable for the treatment of HFH. For example, simvastatin may be co-adminstered with one or more additional drugs which are effective in lowering LDL cholesterol such as HMG-CoA synthase inhibitors; squalene epoxidase inhibitors; squalene synthetase inhibitors (also known as squalene synthase inhibitors), acyl-coenzyme A: cholesterol acyltransferase (ACAT)

inhibitors; probucol; niacin; fibrates such as clofibrate, fenofibrate, and gemfibrizol; cholesterol absorption inhibitors; and bile acid sequestrants. Agents such as aspirin and beta-blockers may also be co-administered with simvastatin. Simvastatin may also be administered in conjunction with therapies such as LDL aphaeresis.

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various changes, modifications and substitutions can be made therein without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated. Likewise, the specific pharmacological responses observed may vary depending upon the particular pharmaceutical carriers employed, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

WHAT IS CLAIMED IS:

1. A method of treating homozygous familial hypercholesterolemia comprising administering a therapeutically effective amount of simvastatin to a person in need of such treatment.

2. The method of claim 1 wherein the daily dosage of simvastatin is more than 40 mg.

3. The method of claim 2 wherein the daily dosage of simvastatin is at least 80 mg.

4. The method of claim 3 wherein the daily dosage of simvastatin is 80 mg.

5. The method of claim 2 wherein the daily dosage of simvastatin is at least 160 mg.

6. The method of claim 5 wherein the daily dosage of simvastatin is 160 mg.

7. The method of claim 1 wherein the simvastatin is administered in a single daily dose.

8. The method of claim 1 wherein the simvastatin is administered in divided daily doses.

9. The method of claim 1 wherein the simvastatin is administered in a controlled time-release formulation.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CHEMICAL ABSTRACTS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. November 1994, Vol. 19:344, pages 1383-9 (1994) (Abstract).	1-9
A	US, 5,393,893 A (KUBELA et al.) 28 February 1995, see entire document.	1-9
A	US, 4,997,849 A (PETUCH et al.) 05 March 1991, see entire document.	1-9

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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AU 9736672	A1	19980202	AU 9736672	A	19970703	
AU 9742289	A1	19980202	AU 9742289	A	19970703	
AU 9743261	A1	19980202	AU 9743261	A	19970703	
GB 9617898	A0	19961009	GB 9617898	A	19960828	(BASIC)
WO 9801116	A1	19980115	WO 97US12426	A	19970703	
WO 9801100	A2	19980115	WO 97US11792	A	19970703	
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US 21420 P 19960709
US 29351 P 19961031
WO 97US12426 W 19970703
WO 97US11792 W 19970703

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PATENT FAMILY:
AUSTRALIA (AU)
Patent (No,Kind,Date): AU 9736672 A1 19980202
THERAPY FOR COMBINED HYPERLIPIDEMIA (English)
Patent Assignee: MERCK & CO INC
Author (Inventor): MITCHEL YALE B; MELINO MICHAEL R
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CA Abstract No: * 128(09)097715J; 128(09)097716K; 128(11)132435S
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Language of Document: English
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METHOD FOR TREATING HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA (English)
Patent Assignee: MERCK & CO INC
Author (Inventor): MITCHEL YALE B; TOBERT JONATHAN A
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PHARMACEUTICAL COMPOSITIONS (English)
Patent Assignee: MERCK & CO INC
Author (Inventor): MITCHEL YALE B; TOBERT JONATHAN A
Priority (No,Kind,Date): GB 9617898 A 19960828; US 21420 P 19960709; US 29351 P 19961031; WO 97US10867 W 19970703
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Derwent WPI Acc No: * C 98-110203; C 98-110207; C 98-145191
Language of Document: English

GREAT BRITAIN (GB)
Patent (No,Kind,Date): GB 9617898 A0 19961009
METHOD FOR TREATING HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA (English)
Patent Assignee: MERCK & CO INC
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Patent Assignee: MERCK & CO INC (US); MITCHEL YALE B (US); MELINO MICHAEL R (US)
Author (Inventor): MITCHEL YALE B (US); MELINO MICHAEL R (US)
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METHOD FOR TREATING HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA (English)

Patent Assignee: MERCK & CO INC (US); MITCHEL YALE B (US); TOBERT JONATHAN A (US)

Author (Inventor): MITCHEL YALE B (US); TOBERT JONATHAN A (US)

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Patent Assignee: MERCK & CO INC (US); MITCHEL YALE B (US); TOBERT JONATHAN A (US)

Author (Inventor): MITCHEL YALE B (US); TOBERT JONATHAN A (US)

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98-145191
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WO 9801100 P 19960709 WO AA PRIORITY CLAIMED
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WO 9801100 P 19960828 WO AA PRIORITY (PATENT)
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WO 97US11792 A 19970703

WO 9801100 P 19980115 WO AK DESIGNATED STATES CITED IN A PUBLISHED APPLICATION WITHOUT SEARCH REPORT (DESIGNATED STATES CITED IN A PUBLISHED APPL. WITHOUT SEARCH REPORT)
AL AM AU AZ BA BB BG BR BY CA CN CU CZ EE GE HU IL IS JP KG KR KZ LC LK LR LT LV MD MG MK MN MX NO NZ PL RO RU SG SI SK SL TJ TM TR TT UA US UZ VN YU AM AZ BY KG KZ MD RU TJ TM

WO 9801100 P 19980115 WO AL DESIGNATED COUNTRIES FOR REGIONAL PATENTS CITED IN A PUBLISHED APPLICATION WITHOUT SEARCH REPORT (DESIGNATED COUNTRIES FOR REGIONAL PATENTS CITED IN A PUBLISHED APPL. WITHOUT SEARCH REPORT)
GH KE LS MW SD SZ UG ZW AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG

WO 9801100 P 19980115 WO A2 PUBLICATION OF THE INTERNATIONAL APPLICATION WITHOUT THE INTERNATIONAL SEARCH REPORT (PUB. OF THE INTERNATIONAL APPL. WITHOUT THE INTERNATIONAL SEARCH REPORT)

WO 9801100 P 19980326 WO DFPE REQUEST FOR PRELIMINARY EXAMINATION FILED PRIOR TO EXPIRATION OF 19TH MONTH FROM PRIORITY DATE

WO 9801100 P 19980520 WO 121 EP: PCT APP. ART. 158 (1) (EP: PCT ANM. ART. 158 (1))

WO 9801100 P 19990604 WO NENP NON-ENTRY INTO THE NATIONAL PHASE IN:
JP 1998505308

WO 9801100 P 20000109 WO NENP NON-ENTRY INTO THE NATIONAL PHASE IN:
CA

WO 9801100 P 20000209 WO 122 EP: PCT APP. NOT ENT. EUROP. PHASE (EP: PCT ANM. NICHT IN EUROP. PHASE EING.)

WO 9801116 P 19960709 WO AA PRIORITY CLAIMED
US 21420 P 19960709

WO 9801116 P 19960828 WO AA PRIORITY (PATENT)
GB 9617898 A 19960828

WO 9801116 P 19961031 WO AA PRIORITY CLAIMED
US 29351 P 19961031

WO 9801116 P 19970703 WO AE APPLICATION DATA (APPL.

DATA)
WO 97US12426 A 19970703

WO 9801116 P 19980115 WO AK DESIGNATED STATES CITED IN A PUBLISHED APPLICATION WITH SEARCH REPORT (DESIGNATED STATES CITED IN A PUBLISHED APPL. WITH SEARCH REPORT)
AL AM AU AZ BB BG BR BY CA CN CZ EE GE HU IL IS JP KG KR KZ LK LR LT LV MD MG MK MN MX NO NZ PL RO RU SG SI SK SL TJ TM TR TT UA US UZ VN YU AM AZ BY KG KZ MD RU TJ TM

WO 9801116 P 19980115 WO AL DESIGNATED COUNTRIES FOR REGIONAL PATENTS CITED IN A PUBLISHED APPLICATION WITH SEARCH REPORT (DESIGNATED COUNTRIES FOR REGIONAL PATENTS CITED IN A PUBLISHED APPL. WITH SEARCH REPORT)
GH KE LS MW SD SZ UG ZW AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG

WO 9801116 P 19980115 WO A1 PUBLICATION OF THE INTERNATIONAL APPLICATION WITH THE INTERNATIONAL SEARCH REPORT (PUB. OF THE INTERNATIONAL APPL. WITH THE INTERNATIONAL SEARCH REPORT)

WO 9801116 P 19980212 WO DFPE REQUEST FOR PRELIMINARY EXAMINATION FILED PRIOR TO EXPIRATION OF 19TH MONTH FROM PRIORITY DATE

WO 9801116 P 19980506 WO 121 EP: PCT APP. ART. 158 (1) (EP: PCT ANM. ART. 158 (1))

WO 9801116 P 19990604 WO NENP NON-ENTRY INTO THE NATIONAL PHASE IN:
JP 1998505391

WO 9801116 P 20000109 WO NENP NON-ENTRY INTO THE NATIONAL PHASE IN:
CA

WO 9801116 P 20000112 WO 122 EP: PCT APP. NOT ENT. EUROP. PHASE (EP: PCT ANM. NICHT IN EUROP. PHASE EING.)

WO 9801119 P 19960709 WO AA PRIORITY CLAIMED
US 21420 P 19960709

WO 9801119 P 19960828 WO AA PRIORITY (PATENT)
GB 9617898 A 19960828

WO 9801119 P 19961031 WO AA PRIORITY CLAIMED
US 29351 P 19961031

WO 9801119 P 19970703 WO AE APPLICATION DATA (APPL. DATA)
WO 97US10867 A 19970703

WO 9801119 P 19980115 WO AK DESIGNATED STATES CITED IN A PUBLISHED APPLICATION WITHOUT SEARCH REPORT (DESIGNATED STATES CITED IN A PUBLISHED APPL. WITHOUT SEARCH REPORT)
AL AM AU AZ BB BG BR BY CA CN CZ EE GE HU IL IS JP KG KR KZ LK LR LT LV MD MG MK MN MX NO NZ PL RO RU SG SI SK SL TJ TM TR TT UA US UZ VN YU AM AZ BY KG KZ MD RU TJ TM

WO 9801119 P 19980115 WO AL DESIGNATED COUNTRIES FOR REGIONAL PATENTS CITED IN A PUBLISHED APPLICATION WITHOUT SEARCH REPORT

			(DESIGNATED COUNTRIES FOR REGIONAL PATENTS CITED IN A PUBLISHED APPL. WITHOUT SEARCH REPORT) GH KE LS MW SD SZ UG ZW AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE BF BJ CF CG CI CM GA GN ML MR NE SN TD TG
WO 9801119	P	19980115 WO A2	PUBLICATION OF THE INTERNATIONAL APPLICATION WITHOUT THE INTERNATIONAL SEARCH REPORT (PUB. OF THE INTERNATIONAL APPL. WITHOUT THE INTERNATIONAL SEARCH REPORT)
WO 9801119	P	19980312 WO DFPE	REQUEST FOR PRELIMINARY EXAMINATION FILED PRIOR TO EXPIRATION OF 19TH MONTH FROM PRIORITY DATE
WO 9801119	P	19980506 WO 121	EP: PCT APP. ART. 158 (1) (EP: PCT ANM. ART. 158 (1))
WO 9801119	P	19990604 WO NENP	NON-ENTRY INTO THE NATIONAL PHASE IN: JP 1998505217
WO 9801119	P	19991110 WO 122	EP: PCT APP. NOT ENT. EUROP. PHASE (EP: PCT ANM. NICHT IN EUROP. PHASE EING.)
WO 9801119	P	20000109 WO NENP	NON-ENTRY INTO THE NATIONAL PHASE IN: CA